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(54) Title: FATTY ACIDS AND THEIR SMALL CHAIN ESTERS AS PENETRATION ENHANCERS IN AQUEOUS SYSTEMS

(57) Abstract

Saturated or unsaturated fatty acids of 8-18 carbon atoms or a C_1-C_4 alkyl ester thereof in an aqueous system are described as skin absorption enhancers resulting in effective and non-irritating transdermal compositions comprising the above in combination with a therapeutically active ingredient.

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FATTY ACIDS AND THEIR SMALL CHAIN ESTERS AS PENETRATION ENHANCERS IN AQUEOUS SYSTEMS

BACKGROUND OF THE INVENTION

This invention relates to pharmaceutical compositions which are useful in effecting transdermal delivery of a therapeutic dose of a therapeutically active ingredient to the systemic circulation of a mammal.

As a specific and preferred application, therapeutically active ingredients or drugs such as opioids may be singled out as preferred active ingredients in such transdermal systems.

Many opioids are known to have poor bioavailability in the mammalian systemic circulation due to extensive initial metabolism of the drug by the liver and intestines. Furthermore, the bioavailability of orally administered opioids may be unpredictable since various factors such as changes in acidity and food content can cause changes in the amount of drug absorbed from the gastrointestinal tract. Also, oral administration does not necessarily ensure good patient compliance.

Parenteral administration of opioids provides better bioavailability than oral administration. However, the various routes of parenteral administration such as intravenous, intramuscular, and subcutaneous delivery are not convenient for chronic therapy. This is particularly true for those opioids which exhibit short biological activity half-lives.

Topical formulations of opioids do not necessarily provide delivery of a therapeutic dose of the drug to the systemic circulation and thus provide

poor or unpredictable bioavailability. Natural oils containing saturated or unsaturated fatty acids have been described in such topical formulations with drugs used for local anesthetic purposes.

Transdermal delivery of opioid drugs to the mammalian systemic circulation have been described as an alternative mode of administration which can provide the following advantages:

1. Improved and predictable bioavailability of the opioid as compared to oral administration since transdermal delivery avoids initial metabolism by the liver and intestines, and unpredictable absorption from the gastrointestinal tract.

2. A stable blood serum level of the drug resulting in a prolonged pharmacological effect similar to intravenous infusion.

3. Easily adjustable dosing rate which provides maximization of efficacy and minimization of side effects.

4. Easily removable drug source which provides rapid cessation of dosing and elimination of the drug from the body fluids.

5. Convenience of dosing which provides improved patient comfort as compared to parenteral administration and the possibility of greater patient compliance as compared to oral administration.

Transdermal drug delivery is distinguished from topical drug delivery by the fact that while a transdermal formulation is specifically designed to provide a predictable and therapeutically significant rate of delivery of the drug to the systemic circulation, a topical formulation is specifically designed to provide a therapeutic effect only to the local area to which the drug is applied. Furthermore, topical formulations are often designed to prevent any systemic delivery of the drug in order to minimize

side-effects. However, even if the topical delivery of a drug does result in systemic absorption, the amount of drug delivery to the circulation is variable and uncontrolled.

European Patent Publication 0 171 742 describes such a system for the transdermal delivery of opioids using saturated or unsaturated fatty alcohols as acids or esters thereof with a carrier or vehicle such as propylene glycol resulting in an organic system, i.e. suspension or gel. The disadvantage of this system is that the use of propylene glycol or other known organic solvents causes irritation to the skin.

It has now been found that saturated or unsaturated fatty acids or esters thereof, such as linoleic acid, is effective as a skin absorption enhancer in purely aqueous systems thus leading to new and effective transdermal compositions without skin irritation.

SUMMARY OF THE INVENTION

Accordingly the present invention relates to a pharmaceutical composition adapted for transdermal delivery of a therapeutically effective amount of a drug to the systemic circulation of a mammal comprising an aqueous suspension containing:

a therapeutically effective amount of a drug or a pharmaceutically acceptable salt thereof;

an effective amount of a saturated or unsaturated fatty acid of 8-18 carbon atoms or a C_1-C_4 alkyl ester thereof, and a pharmaceutically acceptable excipient.

Another aspect of the present invention is a method for the transdermal delivery of a therapeutically effective amount of a drug to the systemic circulation of a mammal which comprises administering to said mammal in an aqueous suspension:

a therapeutically effective amount of a drug or a pharmaceutically acceptable salt thereof;

an effective amount of a saturated or unsaturated fatty acid of C_8-C_{18} carbon atoms or a C_1-C_4 alkyl ester thereof, and a pharmaceutically acceptable excipient.

DESCRIPTION OF PREFERRED EMBODIMENTS

Although the present aqueous transdermal composition encompasses the combination with any drug, the preferred utility of such a composition is with opioids.

By the term "opioid" is meant any natural or synthetic opioid analgesic such as morphine, oxymorphone, fentanyl, meperidine, propoxyphene, or oxycodone; any natural or synthetic narcotic antagonist such as nalmefene, naloxone or naltrexone; any natural or synthetic mixed opioid agonist/antagonist such as nalbuphine, butorphanol, buprenorphine or pentazocine; or any pharmaceutically acceptable salt thereof.

By the term "pharmaceutically acceptable salt" is meant any non-toxic pharmaceutically suitable salt of an opioid which has therapeutic properties in mammals. Preparation of such salts is well-known to those skilled in pharmaceuticals. Pharmaceutically acceptable salts of opioids include acetates, naphthylates, tosylates, succinates, hydrochlorides, palmitates, stearates, oleates, pamoates, laurates, valerates, hydrobromides, sulfates, methane sulfonates, tartrates, citrates, and maleates.

The term "saturated or unsaturated fatty acid of 8-18 carbon atoms" means any such acid or ester thereof effective in enhancing the penetration of a drug through the mammalian skin. Preferred are

linoleic and oleic acids and their C_1-C_4 alkyl esters. Most preferred is linoleic acid.

Pharmaceutically acceptable excipients are additional materials used in the compositions to bind the effective ingredients into a cream or lotion form suitable for administration on the skin per se or through known devices such as bandaids, tapes, patches, and the like. These excipients are, for example, carbopol 934, carbopol 940, carbopol 941, (B. F. Goodrich and Co. they are acrylic acid, water soluble resin polymers, with molecular weights of 3,000,000; 4,000,000; and 1,250,000 respectively); tween 20, (ICI Americas) polysorbate 20 polyoxyethylene 20 sorbitan monolaurate, or other tweens such as tween 40, tween 60, and tween 80, and other pharmaceutically acceptable emulsifiers such as polyethyleneglycol esters, e.g. polyethyleneglycol monolaurates, can also be used.

The effectiveness of the present invention is illustrated by the following examples and results illustrated in table form which compares the permeation of oxymorphone through hairless mouse skin from organic and aqueous enhancer systems containing linoleic acid.

Examples

Non Aqueous Systems

Formulation	Flux (μg/cm²/h)	P (cm/sec x 10^6)	Lag Time (h)	Maximum Solubility (mg/ml)	Maximum* Flux (PxSoly)
LA:PG:TA 20:30:50	66.6	3.49	3.5	130.17	1635.46
LA:PG:TA 10:30:60	51.5	2.65	4.2	93.77	894.29
LA:PG:TA 5:30:65	41.0	2.02	7.6	60.60	440.68
PG:TA 37.5:62.5	< 3	--	--	--	--

*Calculated based on Fick's Law (flux = permeability x concentration gradient: maximum flux = P x solubility of drug in donor solution), assuming Fick's Law holds.

Aqueous Systems

Formulations (containing 5% w/w oxymorphone	Flux (μg/cm²/h)	Lag Time (h)
LA 30% (0.3% Carbopol + 2.5% Tween 20) 70%	667.45	6.8
LA 20% (0.3% Carbopol + 2.5% Tween 20) 80%	636.11	9.3
LA 10% 0.3% Carbopol + 2.5% Tween 20) 90%	672.76	4.3
LA 5% (0.3% Carbopol + 2.5% Tween 20) 95%	543.82	9.5
LA 20% (2.5% Tween 20) 80%	884.46	4.4
0.3% Carbopol	38.31	17
0.3% Carbopol + 2.5% Tween 20	19.73	15.61

Legend

LA = Linoleic Acid

PG = Propylene Glycol

TA = Triacetin

Note: Since the aqueous systems are suspensions, they are constantly providing maximum availability of oxymorphone or permeation (i.e. maximum flux); therefore, to compare permeability data with the organic systems, maximum flux values had to be calculated. Using the premeability coefficients for 0.5% oxymorphone solutions in the linoleic acid:propylene glycol:triacetin mixtures, maximum fluxes were calculated by multiplying the saturation solubility of oxymorphone in the respective system by its corresponding permeability coefficient. However, it should be noted that the aqueous dispersions (5% w/w drug) became depleted of drug causing a plateau in cumulative average concentration versus time graphs,

therefore, higher flux values may be anticipated with the aqueous systems.

As shown in the table, aqueous systems containing the model fatty acid, linoleic acid, effectively enhanced the permeation of a model drug through the skin. The usual dose of oxymorphone is 6-10 mg per day which would be adequately provided by any of the aqueous systems containing linoleic acid from a 10 cm^2 patch.

CLAIMS

1. A pharmaceutical composition adapted for transdermal delivery of a therapeutically effective amount of a drug to the systemic circulation of a mammal comprising an aqueous suspension containing:

a therapeutically effective amount of a drug or a pharmaceutically acceptable salt thereof;

an effective amount of a saturated or unsaturated fatty acid of 8-18 carbon atoms or a C_1-C_4 alkyl ester thereof, and a pharmaceutically acceptable excipient.

2. A composition according to Claim 1, wherein the drug is an opioid.

3. A composition according to Claim 2, wherein the opioid is a natural or synthetic opioid analgesic such as morphine, oxymorphone, fentanyl, meperidine, propoxyphen, or oxycodone; a natural or synthetic narcotic antagonist such as nalmefene, naloxone, or naltrexone; a natural or synthetic mixed opioid agonist/antagonist such as nalbuphine, butorphanol, buprenorphine or pentazocine; or a pharmaceutically acceptable salt thereof.

4. A composition according to Claim 3, wherein the opioid is oxymorphone.

5. A composition according to Claim 1, wherein the fatty acid is linoleic or oleic.

6. A composition according to Claim 1, wherein the aqueous suspension contains up to 0.1-10% by weight of drug.

7. A composition according to Claim 1, wherein the aqueous suspension contains from about 1 to about 30% by weight of a saturated or unsaturated fatty acid of 8-18 carbon atoms or a C_1-C_4 alkyl ester thereof.

8. A composition according to Claim 7, wherein the aqueous suspension contains from about 1 to about 20% by weight of linoleic or oleic acid or a C_1-C_4 alkyl ester thereof.

9. A composition according to Claim 7, wherein the aqueous system contains about 1 to about 30% by weight of linoleic acid.

10. A composition according to Claim 7, wherein the aqueous system contains about 10 to about 20% by weight of linoleic acid.

11. A method for the transdermal delivery of a therapeutically effective amount of a drug to the systemic circulation of a mammal which comprises administering to said mammal in an aqueous suspension:

a therapeutically effective amount of a drug or a pharmaceutically acceptable salt thereof;

an effective amount of a saturated or unsaturated fatty acid of C_8-C_{18} carbon atoms or a C_1-C_4 alkyl ester thereof, and a pharmaceutically acceptable excipient.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 88/01666

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [1]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[4]: A 61 K 47/00

II. FIELDS SEARCHED

Minimum Documentation Searched [2]

Classification System	Classification Symbols
IPC[4]	A 61 K; A 61 L

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [3]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [4]

Category [5]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
A	EP, A, 0171742 (E.I. DU PONT DE NEMOURS AND CO.) 19 February 1986 see the whole document cited in the application --	1-10
A	EP, A, 0160501 (ELI LILLY AND CO.) 6 November 1985 see page 1, line 27 - page 12, line 4; in particular page 9, lines 12-15 --	1-10
A,P	Chemical Abstracts, volume 108, no. 14, 4 April 1988, (Columbus, Ohio, US), T. Loftsson et al.: "The effect of vehicle additives on the transdermal delivery of nitroglycerin", see page 423, abstract 118806u,	
A	& Pharm. Res. 1987, 4(5), 436-7	

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[5] Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
6th September 1988	21 SEP 1988
International Searching Authority: EUROPEAN PATENT OFFICE	Signature of Authorized Officer: P.C.C. VAN DER PUTTEN

Form PCT/ISA/210 (second sheet) (January 1985)

International Application No. PCT/US 88/01666

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☒ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☒ Claim numbers 11, because they relate to subject matter not required to be searched by this Authority, namely:

See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods

2. ☐ Claim numbers ....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim numbers ....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest [1]

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (supplemental sheet (II)) (January 1985)

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 8801666 SA 22712

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 14/09/88 The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0171742	19-02-86	AU-A- 4590585	13-02-86
		JP-A- 61083116	26-04-86
		US-A- 4626539	02-12-86
		AU-B- 574628	07-07-88
EP-A- 0160501	06-11-85	JP-A- 60252410	13-12-85
		AU-A- 4161685	31-10-85
		US-A- 4581225	08-04-86
		AU-B- 570555	17-03-88

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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82